

REMARKS

Claims 5 and 9 have been amended to recite that the process comprises reacting ROH with oxirane at a temperature of 50 to 130°C and in a reaction system containing not more than 5 ppm water. Support is found, for example, at page 19, lines 1-3 of the specification. The remaining amendments are for editorial purposes only, and are not relied upon to distinguish over the applied prior art.

Review and reconsideration on the merits are requested.

Claims 1-4, 7, 8 and 11-13 were rejected under 35 U.S.C. § 112, second paragraph, as not being enabled by the disclosure in the specification. Particularly, the examiner considered that low water content is critical or essential to the practice of the invention, and should therefore be recited in the rejected claims.

Applicants respectfully traverse for the following reasons.

The rejected claims are directed to a product having a high purity characterized in terms of its gel permeation and thin layer properties. These are not process claims but rather define a product. The specification describes how to obtain an oxirane derivative of the requisite purity (i.e., as specified by its gel permeation chromatography property and thin layer chromatography property), and one way, as described in the specification, is to carry out the reaction in a system having a low water content. Therefore, the specification is fully enabling for preparing the claimed product, and it is not necessary to include such process steps in the product claims.

For example, suppose that a claimed invention was directed to compound X having a certain formula and having a purity defined in terms of a narrow melting point range. The specification describes that the compound X having such a narrow melting point range may be

prepared using a recrystallization technique. Under such circumstances, the examiner surely would not insist on claiming compound X (the product) as being prepared by recrystallization, but rather in terms of its formula and melting point range (as needed to define over the prior art). Similarly, in this application, the examiner should not require Applicants to limit their product claims, characterized in terms of chromatographic properties, to oxirane derivatives prepared using a low water content system.

For the above reasons, it is submitted that the originally presented claims fully comply with 35 U.S.C. § 112, second paragraph, and withdrawal of the foregoing rejection is respectfully requested.

Claims 7 and 11 were rejected under 35 U.S.C. §112, second paragraph, as not further limiting the claims from which they depend. Particularly, the examiner considered claims 7 and 11 as being directed to compounds not within the scope of the earlier claims.

Applicants respectfully traverse for the following reasons.

Claims 7 and 11 are product claims directed to an oxirane derivative represented by formula (2). The compound of claim 7 is prepared by aminating or carboxylating an oxirane derivative of formula (1) having a purity as defined in claim 1 or claim 2. Claim 11 is likewise directed to an oxirane derivative represented by formula (2). It is prepared by aminating or carboxylating an oxirane derivative of formula (1) having a purity as defined in claim 3. There is nothing ambiguous in these claims which might suggest that formula (2) is within the scope of formula (1), and it is respectfully submitted that the amended claims as presented herein are in

AMENDMENT UNDER 37 C.F.R. § 1.116
U.S. Appl. No. 09/367,642

proper form. If necessary, Applicants can rewrite claims 7 and 11 to be completely independent of claims 1 and 3 which they refer to.

Withdrawal of the foregoing rejection is respectfully requested.

Claims 1-6 and 8-10 were rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as being obvious over U.S. Patent 4,967,016 to Kemp. Additionally, claims 1-4, 7, 8 and 11-13 were rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over U.S. Patent 5,605,976 to Martinez et al or JP 8-165343 (JP '343).

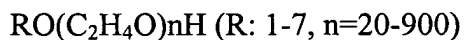
Applicants respectfully traverse for the following reasons.

A characteristic feature of the present invention is that the claimed oxirane derivative has a purity such that a by-product having a molecular weight as much as twice that of the desired compound and a by-product having the same molecular weight as the desired compound are not present.

As to the amendment to process claims 5 and 9, an undesirable by-product is formed when the reaction temperature is too high. See, for example, page 5, lines 10-12 of the present specification.

Concerning the molecular weight, while it is possible to purify in the case of a low molecular weight compound (n is less than 20), it is difficult to purify in the case of a high molecular weight compound (where n is 20 or more). This is described at page 6, line 28 to page 7, line 13 of the specification.

Commercially available oxirane derivatives represented by formula (1):



have the problems (A) to (D) shown below.

(A) (GPC-gel permeation chromatography) By-products having molecular weights as much as twice that of the desired compound → due to water content in the reaction system.

This is described on page 3, line 22 to page 4, line 7, and page 4, lines 13 to 21 of the specification.

(B) (GPC) Compound having a lower molecular weight than the desired compound → by-production of vinyl ether in the reaction system.

This is described on page 5, lines 14 to 25 of the present specification.

(C) (GPC) Deviation of molecular distribution from Poisson distribution → indicating heterogeneous reaction.

This is described on page 6, lines 21 to 25 of the present specification.

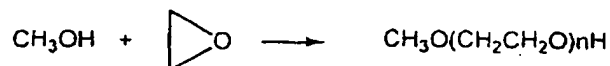
(D) (TLC) Different spots in R_f value → showing the presence of by-products having the same molecular weight as the desired compound.

The present invention relates to a high-purity oxirane derivative not having problems (A) to (D) above.

(A) to (D) are explained in greater detail using the reaction formulas below.

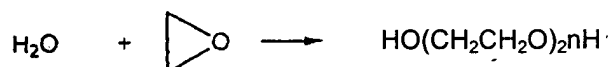
The compound represented by $\text{RO}(\text{CH}_2\text{CH}_2\text{O})_n\text{H}$ is formed as in the reaction 1 below.

(Reaction 1)



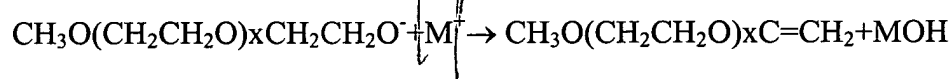
Here, if water is present, a by-product that is a compound having a molecular weight as much as twice that of the desired compound, as shown below is produced - (A)

(Reaction 2)



Furthermore, the compound below is generally formed during the above reaction ((B), (D)) or at the final stage of the above reaction ((C), (D)).

(Reaction 3)



When the compound obtained in the reaction 3 is formed during the formation of the above compound (between o and n; the state before a desired molecular weight is attained), the reaction point with ethylene oxide having OH a terminal disappears so that by-products having a low molecular weight remain. Also, when the compound obtained in the reaction 3 is formed at the final stage, by-products having almost the same molecular weight as the desired compound are produced (x differs in each case.)

The relationship between the above problems and the present claims is as follows

Claim 1:

1) (GPC) the purity of the desired compound (i.e., purity by excluding the above (A) and (B)) is 85% or more; and

2) (TLC) the purity of the desired compound is 98% or more (the above (D) is excluded).

Claim 2: In addition to the requirements of claim 1, the (A) content is not more than 5%.

Claim 3: In addition to the requirements of claim 1 or 2, the deviation shown in (C) is 0.02 or less.

That is, the present invention provides I) a novel high-purity oxirane derivative, not yet heretofore prepared, II) a synthesis process thereof, and III) a terminal-modified oxirane derivative for medical purposes prepared from the high purity oxirane derivative.

Applicants address the applied prior art as follows.

Martinez et al (US 5,605,976):

Martinez provides a process for producing a polyoxyalkylene derivative containing a carboxyl group (e.g., $\text{HOOC-X-O}(\text{CH}_2\text{CH}_2\text{O})_n\text{-X-COOH}$ or $\text{CH}_3\text{O}(\text{CH}_2\text{CH}_2\text{O})_n\text{-X-COOH}$). In comparison with the present invention, it is a process for producing a compound wherein Y in formula (2) is COOH.

Examples 1-7 of Martinez show a production process of the structure shown, e.g., in claim 7.

The starting materials of Martinez are as follows.

MethoxyPEG-OH ($\text{CH}_3\text{O}(\text{CH}_2\text{CH}_2\text{O})_n\text{H}$)

Union Carbide, (Mw: 5,000)

PEG-OH ($\text{HO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{H}$)

Serva (Mw: 20,000, 40,000 or 12,000)

That is, Martinez et al use commercially available starting materials, and there is no disclosure in Martinez et al with respect to purifying the m-PEG or PEG-OH prior to reaction. Under these circumstances, the resulting product necessarily does not meet the purity required by present claim 1.

Example 6 (synthesis of terminal carboxylic acid by using MethoxyPEG-OH of the present invention) and Comparative Example 5 (synthesis of terminal carboxylic acid using commercial MethoxyPEG-OH (ALDRICH)) of the present application explain this difference. The results of liquid chromatography in Example 6 and Comparative Example 5 show that when a commercial MethoxyPEG-OH is used as a starting material, the final product contains a variety of by-products. Because Martinez et al also use a commercial starting material, the compound thus synthesized in Martinez et al does not have a purity (in terms of molecular weight distribution) meeting the terms of present claim 1.

The description on page 3, lines 14-21 of the specification relates to Martinez et al.

From a different perspective, the working examples of Martinez et al indicates a product purity of over 99%, as determined by ^{13}C NMR measurements. Particularly, Martinez describes how to increase the conversion rate of the terminal hydroxyl group to a carboxyl group by using these starting materials. Furthermore, while Martinez does not specifically define purity, it is

presumed as shown below since the measurement of purity in the working examples of Martinez et al was carried out using C^{13} NMR.

- i) $CH_3O(CH_2CH_2O)_{n-1} \underset{a}{CH_2CH_2OH}$
ii) $CH_3O(CH_2CH_2O)_{n-1} CH_2CH_2OCH_2\underset{b}{COOH}$

Since the chemical shifts of a and b are different in C^{13} NMR, the measurement of purity is carried out by comparing the magnitude of the respective shifts.

When the impurity iii) below, identified as (A) above is present in the starting materials, the terminals are converted to carboxyl groups like methoxyPEG (see iv)). However, the conversion rate does not change in this measurement, as shown below, and the chemical shifts a and b of the impurities iii) and iv) cannot be distinguished from the chemical shifts a and b of the starting material and product, respectively. Therefore, the C^{13} NMR data of Martinez et al does not indicate the purity required by present claim 1.

- iii) $HO\underset{a}{CH_2}CH_2O(CH_2CH_2O)_{2n-2}CH_2\underset{a}{CH_2}OH$
iv) $HOOC\underset{b}{CH_2}OCH_2CH_2O(CH_2CH_2O)_{2n-2}CH_2CH_2OCH_2\underset{b}{COOH}$

Kemp (US 4,967,016):

Kemp provides a process for producing an alkylene oxide derivative using a barium phosphate catalyst.

The similar portions to the present invention in Kemp are as follows:

(Col. 4, lines 35-45)

ROH used as a starting material, having 1 to 30 carbon atoms, preferably 6 to 24 carbon atoms, more preferably 8 to 20 carbon atoms.

(Col. 8, lines 15-21)

While not limited thereto, the adduct number (mole) is 1 to 30 or more. The adduct number (mole) is 15 or less in all of the working examples.

(Col. 7, lines 45-58)

It is preferred that water is sufficiently removed from the catalyst and a starting material (reactant). The presence of significant amounts of water (e.g., greater than about 500 ppm (preferably below about 200 ppm) water based on active hydrogen containing reactant) is undesirable. Heating under a reduced pressure is carried out in order to remove water from the mixture of the reactant and catalyst.

1) Purity:

1-1) The only impurity that is mentioned in Kemp is the compound having a molecular weight as much as twice that of the desired compound, which corresponds to (A). Kemp in no way refers to impurities corresponding to (B) to (D).

1-2) While Example 1 of Kemp describes the presence of diolPEG (2.3%) with respect to the impurity corresponding to (A), the other examples of Kemp just describe that the byproduct was PEG.

1-3) While the measurement of the by-product PEG in Kemp is carried out with gas chromatography, it is difficult to apply gas chromatography to analysis of a compound having a molecular weight exceeding 700, since the desired compound is thermally decomposed at a predetermined temperature or higher.

Accordingly, the present invention specifies a GPC analysis, and can detect even the presence of methoxyPEG having no diol component derived from water as shown in Comparative Example 4.

2) Water content:

2-1) The present specification acknowledges that it is possible to remove a water by dehydration under reduced pressure after a catalyst is charged in case that the starting material has a large number of carbon atoms, as a method of removing water from a reaction system (see page 4, lines 22 to line 28 of the specification). However, the present specification states that it is impossible to use this method in the case of the number of carbon atoms ranging 1 to 7, within the scope of the present invention. This is because the boiling point is close to that of water (see page 4, line 28 to page 5, line 4 of the specification).

2-2) Kemp surely states that the water content is 500 ppm or less based on a starting material (reactant) having active hydrogen, as water content in the reaction system. What is described in the present invention is that the water content is 5 ppm or less in the reaction system. The reaction system means a closed space containing a reactor. That is, the present invention requires the control of water content in the closed system (whole reaction system),

since it is difficult to suppress the generation of by-products only by the control of water content of the starting material.

2-3) For reference, in Examples 9, 10 and 11 and Comparative Example G, the water contents in the starting materials (here, the water contents in the catalyst and in the system are not considered) were 24 ppm, 28.9 ppm or less, 40 ppm or less. and 1605 ppm, respectively.

While it is surely an important factor to control water content, the present application shows that it is impossible to obtain the present compound only by control of water content. For example, the present specification indicates that the use of an acid catalyst results in by-production of cyclic polyether, making it difficult to obtain the desired compound at the requisite purity. Furthermore, the viscosity of the system is high due to the high molecular weight of the desired compound (see page 19, lines 11 to 28).

Thus, the present invention is completely different from Kemp, which just defines water content and a catalyst.

The feature of the present invention resides in a novel MethoxyPEG-OH without any impurities mentioned in (A) to (D).

JP '343:

JP '343 surely shows a GPC chart of a starting material. However, since this GPC chart has a logarithmic axis in the abscissa axis, it is clear that this chart was obtained by recalculating in accordance with the logarithm of the molecular weight obtained from a calibration curve.

Thus, it is impossible to determine the presence or absence of a byproduct only from the recalculated peak.

It is understood that the MethoxyPEG-amine synthesized using the starting material shown in Fig. 3 of JP '343 has a large amount of impurities. In Example 1 of JP '343, high-purity MethoxyPEG-amine is obtained by purifying with an ion exchange method (ion exchange type liquid chromatography). However, since the liquid chromatography shown in Fig. 4 is a separation using an ionic column, it just separates into an ionic material and a nonionic material. In other words, if there are different materials having the ionic property, they are not separated as an impurity. In the impurity having a different molecular weight distribution or impurity having the same molecular weight but having a different distribution, which has an OH group at the terminal, the OH group is converted into an amine like MethoxyPEG-OH. Accordingly, the ionic property is almost the same therebetween, and it is impossible to analyze impurities with such ion exchange type liquid chromatography.

In Examples 8 and 9 and Comparative Example 7 of the present application, MethoxyPEG-amines were synthesized using MethoxyPEG-OHs of the present invention and a commercially available MethoxyPEG-OH. While the thus-obtained MethoxyPEG-amines showed almost the same purity in an amine-value converted purity, when they were further converted into a block polymer, their physical properties were greatly different from each other. Moreover, Comparative Example 8 shows that this difference originates, for example, from diol components having different molecular weights.

AMENDMENT UNDER 37 C.F.R. § 1.116
U.S. Appln. No. 09/367,642

In view of the above, the present compounds have a high purity in all senses, are novel, and are very useful in the medical field.

For these above reasons, it is submitted that the high purity oxirane derivatives and process for preparing the same are patentable over Kemp, Martinez et al and JP '343, each taken alone or in combination, and withdrawal of the foregoing rejections is respectfully requested.

Claims 1-13 were rejected under 35 U.S.C. § 102(a) as being unpatentable over Martinez et al or JP '343 in combination with Kemp.

The reason for rejection was that it would have been obvious to produce methoxy PEG according to Martinez et al or JP '343 in the absence of water as taught by Kemp to maintain a narrow molecular weight distribution.

Applicants reply on the response above with respect to the rejections over Kemp and over Martinez et al or JP '343 above. None of the cited references discloses an oxirane derivative or process for preparation thereof having a purity as specified in present claim 1. Therefore, the combination of Martinez et al or JP '343 with Kemp would also not achieve the present invention.

Withdrawal of the foregoing rejection is respectfully requested.

Withdrawal of all rejections and allowance of claims 1-15 is earnestly solicited.

In the event that the Examiner believes that it may be helpful to advance prosecution of this application, the Examiner is invited to contact the undersigned at the local Washington, D.C. telephone number indicated below.

AMENDMENT UNDER 37 C.F.R. § 1.116
U.S. Appln. No. 09/367,642

Applicants hereby petition for any extension of time which may be required to maintain the pendency of this case, and any required fee, except for the Issue Fee, for such extension is to be charged to Deposit Account No. 19-4880.

SUGHRUE, MION, ZINN,
MACPEAK & SEAS, PLLC
2100 Pennsylvania Avenue, N.W.
Washington, D.C. 20037-3213
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

Date: Monday, April 16, 2001

Respectfully submitted,

Lee C. Wright
(LEE C. WRIGHT)
Ref No. 41,441

for Abraham J. Rosner
Registration No. 33,276